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CASE REPORT

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Acute Generalized Exanthematous Pustulosis in Pediatric Patients: A Rare Drug Reaction from the Neonatal to Adolescent Period

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ABSTRACT

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, and severe cutaneous adverse reaction, primarily associated with drug exposure. AGEP is characterized by the rapid onset of edema and erythema, followed by the appearance of numerous non-follicular, sterile pustules, which subsequently evolve into desquamation. The reaction typically develops within 1 to 11 days after drug exposure and resolves spontaneously within approximately 15 days. Acute localized exanthematous pustulosis (ALEP) is a localized variant of AGEP, in which pustular lesions are confined to one or more specific areas of the skin.

In this article, we present three pediatric cases with rare manifestations of AGEP and ALEP, diagnosed based on the EuroSCAR criteria. The cases include a male neonate with localized pustular involvement of the scalp and forehead triggered by phenobarbital, a 7-year-old male diagnosed with AGEP following anti-thymocyte globulin (ATG) administration with back and arm involvement, and a 15-year-old female with a diagnosis of ALEP after postoperative use of amoxicillin-clavulanic acid. These cases highlight the diverse clinical spectrum of AGEP and ALEP in pediatric patients and underscore the importance of early diagnosis and appropriate management.

In conclusion, while AGEP and ALEP are rare in pediatric patients, they should be considered in children of all ages presenting with characteristic pustular eruptions following suspected drug exposure. Early recognition and differentiation from other pustular dermatoses are essential for timely and appropriate management.

Keywords: Acute generalized exanthematous pustulosis, acute localized exanthematous pustulosis, cutaneous adverse reaction, drug eruption

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is a rare, acute, and severe cutaneous adverse reaction, primarily associated with drug exposure. However, other potential triggers, including infections, vaccines, and even spider bites, have been reported. The most commonly implicated drugs include penicillins, levofloxacin, trimethoprim-sulfamethoxazole, clindamycin, nimesulide, allopurinol, paracetamol, ibuprofen, docetaxel, finasteride, infliximab, bemiparin, and heparin. AGEP is characterized by the rapid onset of edema and erythema, followed by the appearance of numerous non-follicular, sterile pustules, which subsequently evolve into desquamation. The reaction typically develops within 1 to 11 days after drug exposure and resolves spontaneously within approximately 15 days. While AGEP is considered self-limiting, it can be accompanied by fever exceeding 38°C. Laboratory findings often include leukocytosis, neutrophilia, and mild eosinophilia. The condition is more frequently observed in wom-

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en, with an average age of onset reported to be 56 years. (1,2). Acute localized exanthematous pustulosis (ALEP) is a localized variant of AGEP, in which pustular lesions are confined to one or more specific areas of the skin (3). The most commonly affected site is the face, followed by the trunk and upper extremities (4). The EuroSCAR scoring system, developed to standardize the diagnosis of AGEP/ALEP, evaluates morphology, distribution, desquamation, systemic symptoms, and histopathological features, and classifies cases based on the total score as definite (>8 points), probable (5-7 points), possible (3-4 points), or excluded (<3 points).

In this article, we present three pediatric cases with rare manifestations of AGEP and ALEP, diagnosed based on the EuroSCAR criteria (EuroSCAR scores of the patients are shown in Table I) The cases include a male neonate with localized pustular involvement of the scalp and forehead triggered by phenobarbital, a 7-year-old male diagnosed with AGEP following anti-thymocyte globulin (ATG) administration with back and arm involvement, and a 15-year-old female with a diagnosis of ALEP after postoperative use of amoxicillin-clavulanic acid. These cases highlight the diverse clinical spectrum of AGEP and ALEP in pediatric patients and underscore the importance of early diagnosis and appropriate management.

Case Presentations

Case 1

A 19-day-old male infant presented with pustular lesions on the scalp and forehead that had been present for

Table I: EuroSCAR AGEP/ALEP Diagnostic Validation Score

		Case 1	Case 2	Case 3
Morphology				
Pustules				
Typical	+2	+2	+2	+2
Compatible	+1			
Insufficient	0			
Erythema				
Typical	+2	+2	+2	+2
Compatible	+1			
Insufficient	0			
Distribution/Pattern				
Typical	+2	+2	+2	+2
Compatible	+1			
Insufficient	0			
Postpustular Desquamation				
Yes	+1	+1	+1	+1
No/Insufficient	0			
Course				
Mucosal Involvement				
Yes	-2			
No	0	0	0	0
Acute Onset				
Yes	0	0	0	0
No	-4			
Resolution <15 days				
Yes	0	0	0	0
No	-4			
Fever >38°C				
Yes	+1		+1	
No	0	0		0
Polymorphonuclear leukocytes >7000/mm³				
Yes	+1			
No	0	0	0	0
Histology				
Findings indicative of other diseases	-10			
Non-descriptive/no histological examination	0	0		0
Polymorphonuclear cell exocytosis	+1			
Subcorneal and/or intraepidermal pustules without spongiosis or other specific characteristics, with papillary edema	+2		+2	
Spongiform subcorneal and/or intraepidermal pustules with papillary edema	+3			
EuroSCAR AGEP/ALEP Diagnostic Validation Score		7	10	7

The EuroSCAR scoring system, developed to standardize the diagnosis of AGEP/ALEP, evaluates morphology, distribution, desquamation, systemic symptoms, and histopathological features, and classifies cases based on the total score as definite (>8 points), probable (5-7 points), possible (3-4 points), or excluded (<3 points).

15 hours. He had been diagnosed with arthrogryposis at 10 days of age due to restricted lower extremity extension. Two days prior to the onset of lesions, phenobarbital was initiated for epileptiform waves detected on EEG, and the pustular eruption appeared following the third dose. The patient remained afebrile, with no lymphadenopathy or mucosal involvement, and his vital signs and laboratory results were within normal limits. Dermatological examination revealed multiple non-follicular pustules with subsequent desquamation (Figure 1A,B). Given the neonatal status and characteristic lesion presentation, a biopsy was not performed. Common neonatal pustular dermatoses such as erythema toxicum neonatorum, transient neonatal pustular melanosis, and bacterial folliculitis were excluded based on clinical presentation and laboratory findings. Bacterial cultures and viral PCR (including HSV and CMV) were negative. No patch testing or in vitro diagnostic tests were performed due to the patient's age. Based on the EuroSCAR criteria, the patient received a score of 7, leading to a diagnosis of probable ALEP. Phenobarbital was discontinued and replaced with levetiracetam, while topical hydrocortisone acetate (0.5%) was initiated. The lesions resolved completely within five days without recurrence.

Case 2

A 7-year-old male patient with a RAG1 gene defect developed pustular eruptions on an erythematous background (Figure 2A,B), predominantly affecting the trunk and extremities, following anti-thymocyte globulin (ATG) administration as part of the conditioning regimen prior to bone marrow transplantation. The lesions began approximately a day after ATG administration. The patient reported no itching. Viral and bacterial screening, including CMV PCR and EBV PCR and blood cultures, showed no evidence of infection. The lesions exhibited a progressive spread, consistent with acute generalized exanthematous pustulosis (AGEP). Histopathological examination revealed focal collections of neutrophils in the granular layer, mild perivascular lymphocytic infiltration, and scattered neutrophils with occasional eosinophils in the superficial dermis. Additionally, intraepidermal pustules and papillary dermal edema were observed, without evidence of spongiosis. These findings support a EuroSCAR histopathology score of 2. Representative histopathological images are provided in Figure 2C-E. Treatment with systemic methylprednisolone (2 mg/kg) led to complete resolution of the lesions within 48 hours.

Case 3

A 15-year-old female patient underwent right thyroid lobectomy due to multiple nodules in the right thyroid lobe and a suspicious fine needle aspiration biopsy result. Postoperatively, amoxicillin-clavulanic acid was initiated. Twenty-four hours after the start of antibiotic therapy, pustular lesions on an erythematous background (Figure 1H) developed on the anterior chest. The patient did not report any itching. There was no evidence of mucosal or

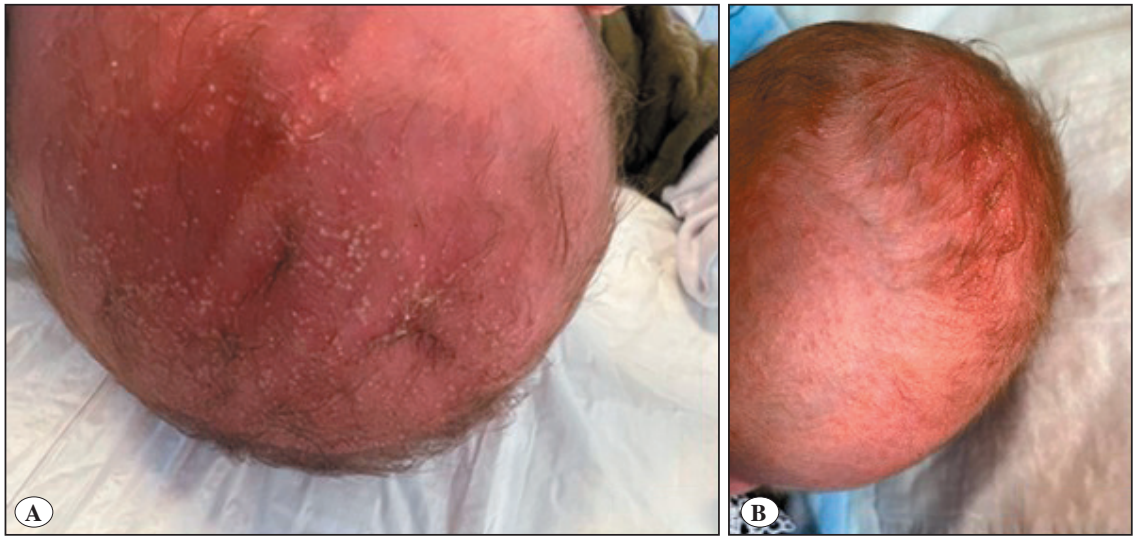

Figure 1. A,B) Multiple pustular lesions on an erythematous background in the scalp region, with focal areas of desquamation accompanying pustular lesions in the forehead and scalp.

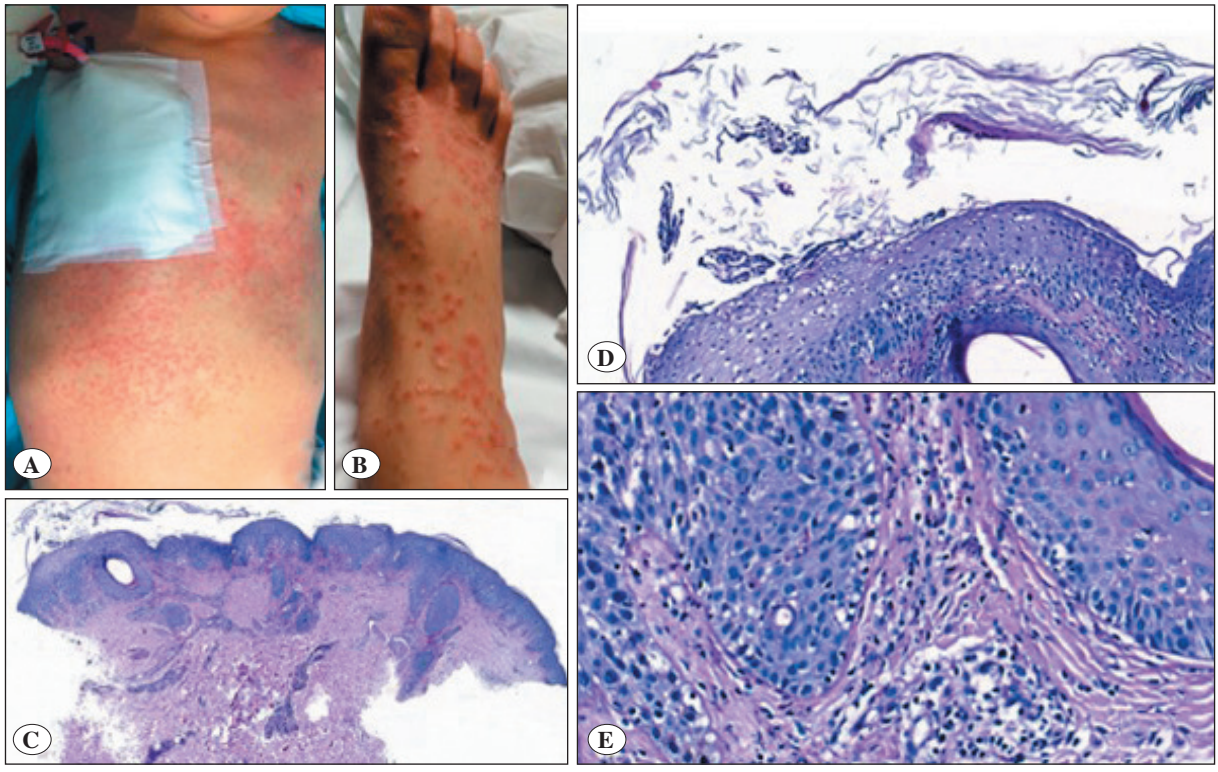

Figure 2. A,B) Pustular rash on an erythematous background on the anterior chest and dorsum of the foot. **C)** Acanthosis and orthokeratosis in the epidermis, with mild inflammatory cell infiltration in the superficial dermis. H&E x4.6. **D)** A pustular focus characterized by clusters of neutrophilic leukocytes above the granular layer of the epidermis. H&E x19.8. **E)** Neutrophil and occasional eosinophil exocytosis in the epidermis near the pustular focus. H&E x49.3.

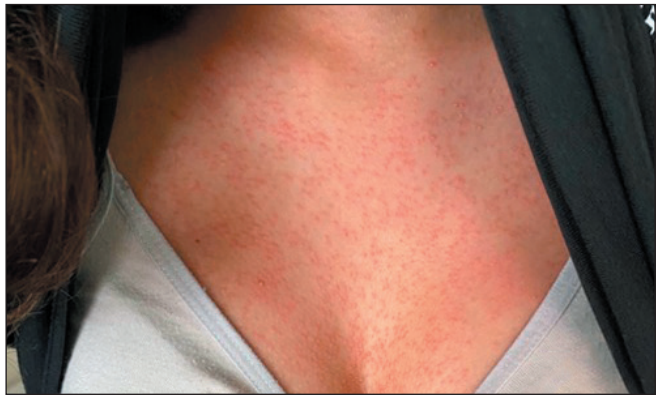

Figure 3. Non-follicular pustular eruption on an erythematous background on the anterior chest.

systemic organ involvement upon examination. Amoxicillin-clavulanic acid was discontinued, and local corticosteroid treatment along with antihistamines was initiated, as the rash remained confined to the anterior chest. The antibiotic had been initiated as postoperative prophylaxis, and no alternative antibiotic therapy was administered. A biopsy was not performed due to patient refusal. No diagnostic test such as patch testing or in vitro assay was performed due to patient refusal. Based on the EuroSCAR criteria, the patient scored 7 points, leading to a diagnosis of probable acute localized exanthematous pustulosis (ALEP). The rash regressed by the third day, with desquamation, following withdrawal of the suspected agent and initiation of local treatment.

DISCUSSION

Acute generalized exanthematous pustulosis (AGEP) is a severe cutaneous adverse reaction, predominantly drug-induced, and characterized by the rapid onset of sterile pustules on an erythematous, edematous skin background, often accompanied by fever and neutrophilia. While approximately 90% of the cases are associated with drug exposure, bacterial, viral, and parasitic infections have also been implicated in its etiology (5). AGEP is more frequently reported in adults, with a predominance in females; however, pediatric cases are predominantly observed in males.

Several immunological pathways contribute to the pathogenesis of AGEP, including increased interleukin-8 (IL-8) secretion, which promotes neutrophil recruitment and survival. Patch testing and in vitro assays support the hypothesis that AGEP is a T cell-mediated, delayed hypersensitivity reaction triggered by specific drugs or other external factors (5).

Additionally, mutations in the IL36RN gene have been suggested as a potential genetic predisposition to AGEP (5,6). Acute localized exanthematous pustulosis (ALEP) shares clinical and histological features with AGEP, including the progression of lesions from erythema to pustules and subsequent desquamation. The triggers of ALEP are similar to those of AGEP, with antibiotics being the most commonly reported culprit. However, ALEP typically lacks systemic involvement, distinguishing it from AGEP. The diagnosis of AGEP relies on a combination of clinical and histopathological criteria, as cases with overlapping presentations or associations with other disease processes have been reported. In a review of pediatric cases of ALEP by Akbayrak et al., amoxicillin-clavulanic acid was identified as the causative agent in one patient, similar to our case, while cefixime-induced ALEP was reported in an 11-year-old girl (7). Şenbaba et al. described a pediatric AGEP case following amoxicillin-clavulanic acid, confirmed by histopathology and resolved within four days after drug withdrawal (8). In a 10-year retrospective review by Lee and Koh from Singapore, eight pediatric AGEP cases were evaluated. Five of these were associated with infections, including *Epstein-Barr virus* and *Mycoplasma pneumoniae*, while the remaining three were drug-induced, with paracetamol and amoxicillin-clavulanic acid being the identified agents (9). Kutluğ et al. reported a pediatric AGEP case induced by paracetamol, with a high EuroSCAR score and favorable response to systemic corticosteroids (10). A comparative summary of the demographic and clinical features of these reported cases alongside those in the current study is provided in Table II.

Table II: Comparison of Pediatric AGEP and ALEP Cases in the Literature and the Present Study

Cases	Age	Sex	Diagnosis	Systemic Symptom	Mucosal Involvement	Affected Areas	Etiologic Agent	Resolution Time
Present Case 1	19 days	Male	ALEP	No	No	Scalp, forehead	Phenobarbital	5 days
Present Case 2	7 yrs.	Male	AGEP	No	No	Trunk, extremities	Anti-thymocyte globulin (ATG)	2 days
Present Case 3	15 yrs.	Female	ALEP	No	No	Anterior chest	Amoxicillin-clavulanic acid	3 days
Akbayrak et al* (2022) (7)	9-14 yrs. (9 cases)	3 Female 6 Male	ALEP	3/9 cases	Not detected in index case, not reported in others	Face, penis, extremities	Cefixime, lamotrigine, amoxicillin-clavulanate, herbal remedies	7-30 days (9 cases)
Şenbaba et al. (2014) (8)	4 yrs.	Male	AGEP	Fever	No	Hands, flexural areas, feet	Amoxicillin-clavulanic acid	12 days
Lee and Koh (2021) (9)	20 months.-16 yrs. (8 cases)	3 Female 5 Male	AGEP	7/8 positive	1/8 cases	Face trunk back limbs flexures	EBV, *Streptococcus*, Influenza A, Possibly ceftriaxone, TMP-SMX, amoxicillin-clavulanate	3-10 days
Kutluğ et al. (2017) (10)	10 months	Male	AGEP	Fever, leukocytosis	No	Inguinal region, armpit, extremities	Paracetamol	Not reported

AGEP: Acute generalized exanthematous pustulosis, **ALEP:** Acute localized exanthematous pustulosis, **ATG:** Anti-thymocyte globulin, **EBV:** Epstein-Barr virus, **TMP- SMX:** Trimethoprim sulfamethoxazole.

Resolution time refers to the number of days until pustular eruption subsided following withdrawal of the suspected agent and/or initiation of treatment. *The cases presented by Akbayrak et al. include both an index case and a literature review of eight pediatric ALEP cases.

The neonatal presentation of AGEP and ALEP remains exceptionally rare. Kaplan and Topal reported a case of a 25-day-old neonate with ALEP secondary to Epstein-Barr virus (EBV) viremia, with a EuroSCAR score of 11. The lesions resolved within nine days following treatment with topical steroids and emollients (11). However, that case was associated with viral infection rather than drug exposure. To our knowledge, no neonatal ALEP cases triggered by medications have been previously reported in the literature. Therefore, our first case may represent one of the earliest documented instances of drug-induced ALEP in the neonatal period. In our case, the eruption was localized, not accompanied by systemic symptoms, and showed rapid resolution following drug withdrawal. The EuroSCAR scoring system, which assesses AGEP based on morphology, clinical course, and histology, has not yet been specifically adapted for pediatric patients (12). This tool classifies cases as definite, probable, possible, or no AGEP. While mucosal involvement is mild and present in approximately 20% of cases, systemic symptoms such as fever and leukocytosis are frequently observed. As AGEP and ALEP are self-limiting conditions, treatment primarily involves discontinuation of the offending drug and supportive care, including topical corticosteroids, antipyretics, and antihistamines (13).

A major limitation of this study was the absence of histopathological confirmation in two cases and the lack of confirmatory diagnostic testing to identify the causative agents. Nevertheless, the clinical findings, EuroSCAR scores (7 points), and favorable treatment responses strongly support the diagnoses. In pediatric patients, differential diagnoses of pustular eruptions include varicella, pustular psoriasis, impetigo, scabies, and neonatal pustular dermatoses, highlighting the need for comprehensive clinical and microbiological evaluation.

In conclusion, although AGEP and ALEP are uncommon in children, they should be considered in patients of all pediatric age groups presenting with characteristic pustular eruptions following suspected drug exposure. Prompt recognition and differentiation from other pustular dermatoses are crucial for effective management.

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Conflicts of Interest

All authors declare that there is no conflict of interest.

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